Mechanism of Luminal Enlargement in PTCA and Restenosis:

A Histopathological Study of Necropsied Coronary Arteries
Collected from Various Centers in Japan

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Necropsy studies of coronary arteries were made in 14 patients who died after percutaneous transluminal coronary angioplasty (PTCA). Eight patients died shortly after PTCA, while the other six patients died some considerable time later. A total of 9,920 serial step sections of necropsied coronary arteries at the site of PTCA were prepared and examined histopathologically by light microscope to determine the mechanism of luminal enlargement in PTCA, as well as the occurrence of restenosis. Of the eight patients who died shortly after PTCA, two had disruption of the intima and the media in the arterial wall located opposite the site that had atheroma, in spite of the fact that the former wall is more normal than the latter. Dissection of the media was camed out in four patients and intimal desquamation performed in six. All the patients revealed fresh thrombus formation. Of the six patients who survived for a long time after PTCA was performed, two had disruption of the intima and the media located opposite the site with atheroma. In one, the media was dissected and in another, intimal desquamation was camed out. In one patient, release of atheroma into the lumen was suspected. Proliferation of intimal cells was revealed in three patients indicating that restenosis had occurred. No compression of the atheroma was observed in any of the 14 patients.

The above findings led to the conclusion that the mechanisms of luminal enlargement in PTCA are: 1) intimal and medial disruption in the arterial wall located opposite the atheroma; 2) medial dissection; 3) intimal desquamation; 4) release of atheroma into the lumen; and 5) any combination of 1) – 4).

Key words:
- Percutaneous transluminal coronary angioplasty (PTCA)
- Mechanism of PTCA
- Coronary arterial dissection
- Thrombus
- Proliferation of intimal cells

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With regard to restenosis, all patients in our study revealed fresh thrombus formation, which suggests the early occurrence of restenosis after PTCA. Three of the six patients who survived long after PTCA showed proliferation of intimal cells. This suggests the possibility that even if the stenosed artery were dilated by PTCA, stenosis may have again occurred as a result of excessive proliferation of intimal cells repairing arterial lesions.

At present, an increasing number of patients with ischemic heart disease undergo percutaneous transluminal coronary angioplasty (PTCA). This technique allows the amelioration of ischemia without open heart surgery. Thus, PTCA has proven to be efficacious in a large number of patients with the disease. Extensive histopathological studies of the site where PTCA was performed have not been reported, so the mechanisms of luminal enlargement in PTCA remain unclear. Furthermore, in approximately 30%–40% of patients who underwent PTCA, restenosis occurred within several months. To clarify these problems, we conducted a multi-center study of patients who had undergone PTCA, and in whom necropsy was performed. Important findings on the mechanism of luminal enlargement in PTCA and restenosis were obtained and are reported here.

SUBJECTS AND METHODS

From 1985 through 1986, questionnaire surveys were distributed at 198 university hospitals and general hospitals nationwide, to determine whether they had conducted necropsy studies following PTCA. Of the 198 institutions contacted, 142 responded (71.7%), and 40 necropsy cases were reported. We were permitted to make an investigation in 22 of the 40 cases and from these we selected 14 cases, where it was possible to evaluate arterial lesions histopathologically. The breakdown of the 14 cases is shown in Table I. Eight patients died shortly after PTCA, their deaths occurring from 30 minutes to seven days after the procedure. The deaths of the other six patients occurred after a longer period of time, ranging from 16 days to two years and eight months. In preparation for pathological exami-

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<tr>
<th>Case</th>
<th>Diagnostic</th>
<th>% Diameter Stenosis</th>
<th>Interval ~Death</th>
<th>Mode of Death</th>
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<tr>
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<td>7d.</td>
<td>CHF, VT</td>
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<td>14. (60-F)</td>
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Emergency = emergency PTCA; Elective = Elective PTCA; M = male; F = female; Diag = diagnosis; AMI = acute myocardial infarction; OMI = old myocardial infarction; AP = angina pectoris; Ca. = cancer; Ao. Aneu. = aortic aneurysm; LMT = left main truncus; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; D = day; H = hour; M = month; CHF = congestive heart failure; VT = ventricular tachycardia; VF = ventricular fibrillation

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Fig. 1. Case 6

A: The patient had angina pectoris. A 90%–99% narrowing is present in the left anterior descending artery.

B: PTCA produced a slight luminal enlargement at the site indicated by the arrow.

C: Repeated inflation induced a complete occlusion of the artery at the site of PTCA.

D: Infarction is observed in the left ventricular anterior wall and in the anterior portion of the ventricular septum.

E: Histopathological picture of the occluded site of the left anterior descending artery (stained with Masson’s trichrome). Fresh thrombus formation is evident between the mark * and the arrows, with the presence of hemorrhaging in the atheroma (Ath). Intimal collagen fibers at the site * reveals disruption. This leads to the postulation that PTCA may have caused “rupture of plaque-thrombus formation”\(^1\) which are commonly observed at the onset of myocardial infarction. Although the lumen was enlarged due to intimal and medial disruption (**), some portions of the coronary arterial wall are made up of only the adventitia (the arrow A). Medial dissection (D) is also seen.

F: The site peripheral to the site shown in E. (stained with Elastica van Gieson). Intimal and medial disruption is identified in the arterial wall (*) located opposite the site with atherosclerotic plaque (Pl). Although luminal enlargement is seen, some portions of the arterial wall are made up of only the adventitia (A).

G: Intimal desquamation is present (arrow), thereby slightly enlarging the lumen.
nation, a total of 9,920 serial step sections (142–1,350 from each patient) were prepared from the coronary arteries at the site where PTCA had been performed. For light microscopy, the sections were stained with Masson’s trichrome, Elastica van-Gieson or Hematoxylin-Eosin.

RESULTS
Results of the histopathological examination in representative cases are described.

Case 6: R.O. A 61-year-old man

This patient had unstable angina pectoris. Coronary arteriography (CAG) showed 90%-99% narrowing in the left anterior descending artery before PTCA (Fig. 1A). PTCA produced a slight dilation of the stenosed artery, as indicated by the arrow in Fig. 1B. During repeated inflation, however, this site was completely occluded (Fig. 1C). Although aortocoronary bypass was performed within a short time, this patient developed acute anterior myocardial infarction two days afterwards, then died.

Necropsy findings: Heart weight was 540g. Necrosis was observed in the left ventricular

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Fig. 3. Case 7
A: The patient with angina pectoris. A 90% narrowing is present in the left circumflex artery (arrow).
B: “Filling delay” after PTCA.
C: Insufficient “wash out” of contrast material.
D: Occlusion occurred in segments No. 5 and No. 6 of the left coronary artery during PTCA.
E: Left main truncus (No. 5). Splitting (arrow) is apparent from the intima to the media.
F: Next to the splitting seen in E, medial dissection, approximately 4 cm in length, is present. Hemorrhaging into the dissected lumen (H) has led to compression and occlusion of the lumen.
G: Segment No. 13 of the left circumflex artery at the site of PTCA. Only L is the pre-existing lumen, and the lumen-like channel indicated by the arrows are splits in the intima.
H: A detail of the site T shown in G. Fresh thrombus formation (T) is evident.
I: The site approximately 9 mm peripheral to the site shown in G. This is one of the sites where stenosis of the lumen is most distinctive in segment No. 13. Medial dissection (D) is seen. The wall of the false lumen is made up mostly of the adventitia.

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Fig.4. Case 7
Segment No. 13 of the left circumflex artery at the site of PTCA.
A: Proximal portion
D: Distal portion
The sites A, B, C and D are located at intervals of 400 μm. A', B' and C' are details of A, B and C, respectively. No compression of atheroma (A) or foam cells (F) is observed, and intimal disruption (D & D') is identified. Disrupted site (D') serves as an entry (E) into the dissected lumen (D). Fresh thrombus formation (T) is also observed.

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The patient was hospitalized for acute myocardial infarction. On the day following the onset of the disease, PTCA was performed, thereby achieving a 100% narrowing of the left anterior descending coronary artery, to 70%. The patient, however, died from pneumonia two months later.

A: Proximity of the left anterior descending artery (stained with Elastica van Gieson).

Intimal and medial disruption (the arrow D) is present. L: lumen, Ath: atheroma

B, C: Details of the upper half of A (C: stained with Masson's trichrome)

The lumen already shows restenosis, resulting from excessive proliferation of intimal cells.

D: A detail of the site * shown in C (×100). Numerous intimal cells are observed.

Case 7: K.H. A 40-year-old man

This patient had angina pectoris. There was a 90% narrowing in segment 13 of the left circumflex artery (Fig. 3A), and PTCA was performed. Balloon inflation was repeated three times, but "filling delay" (Fig. 3B) and insufficient "washout" of contrast material (Fig. 3C) were observed. This suggested that PTCA had failed to provide satisfactory dilation of the lumen. During PTCA, this patient complained of chest pain. An arteriogram was then taken, thereby revealing a complete occlusion in segment 6 (Fig. 3D). Although aortocoronary bypass was immediately performed, this patient experienced low output syndrome due to acute myocardial infarction, and died 36 hours after PTCA.

Necropsy findings: Heart weight was 420g. At the base of the heart, infarction was localized in the anterior part of the ventricular septum and the left ventricular anterior wall, whereas at the apex, it ranged over almost the whole circumference of the left ventricle. Medial dissection, approximately 4 cm in length, was present in segments 5 and 6 of the left coronary artery, which led to hemorrhaging into the dissected lumen. As a result, the lumen was compressed and occluded (Fig. 3F). A crack, 0.1-0.2 mm in width, was observed between the intima and the media in the wall of the dissected coronary ar-
Fig. 6. Case 10
The patient was hospitalized for acute anteroseptal myocardial infarction.
A: A 90% narrowing of the left anterior descending artery (arrow).
B: Although PTCA reduced the narrowing to 25%, he died from pneumonia combined with congestive heart failure.
C: The site of the coronary artery, 3-4 mm from the site of PTCA. The lumen L shows contrast material (I) used in coronary arteriography at necropsy (stained with Elastica van Gieson).
D: The coronary artery at the site of PTCA (stained with Elastica van Gieson). Besides the lumen L, the lumen-like channel L' is identified.
E: A detail of the area * shown in D (stained with Elastica van Gieson, x 16). Contrast material (I) and thrombus (Th) are deposited over the surface of the false-lumen L'. The false-lumen L' is considered not to be an artifact created during the preparation of the tissue specimens. It is thought that atheroma in the channel L' was collapsed and released into the pre-existing lumen L.

tery (Fig. 3E). This lesion was thought to have resulted from the use of the guide wire. The site of PTCA showed intimal disruption (Fig. 3G and Figs. 4A-D) and medial dissection (Fig. 3I) in many places, as well as a fresh thrombus in the cracked intima (Figs. 3G & H and Figs. 4C & C'). A total of 1,350 tissue sections of the circumflex artery were investigated, but no compression of the atheroma was observed (Fig. 4).

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Fig. 7. Case 12
Coronary arteriogram before (A) and after PTCA (B). Before PTCA (Fig. A), about 80% stenosis of the proximal portion of the left anterior descending artery is observable (arrow) and after PTCA (Fig. B), the stenosis has decreased to 50% of the original lumen.
Histopathologic finding at the site of PTCA seven months after the procedure.

C: There is no evidence that suggests the presence of compressed atheroma but, instead, fragmentation of the elastic fibers is seen (arrows). (Elastica van Gieson stain) The site at * in this coronary artery section was cut open during the autopsy.

D: Enlarged view of Fig. C. Arrows indicate fragmented elastic fibers in the thickened intima.

E: Same site as in Fig. D (Masson's trichrome stain).

F: Enlarged view of the area between the two arrows. Proliferation of smooth muscle and other intimal cells, which is prominent at the site of the fragmented elastic fiber, can be seen (Masson's trichrome stain).

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Case 9: Y.H. A 64-year-old man
This patient was hospitalized for acute anteroseptal myocardial infarction. On the day following the onset of the disease, CAG was performed, which revealed an occlusion in the proximal portion of the left anterior descending artery. The occluded site was dilated by PTCA, thereby reducing the narrowing to approximately 70%. The course of the patient’s recovery was satisfactory, but he died from deglutition pneumonia two months later.

Necropsy findings: Heart weight was 360 g.

Slight dilation was present in both ventricles. An old infarction was observed in the left ventricular anterior wall and in three quarters of the anterior portion of the ventricular septum. The necropsy at the site of the PTCA, i.e., in the proximal portion of the left anterior descending artery, showed disruption of the intima and the media in the arterial wall located opposite the atheroma (arrow D in Fig. 5A), even though this wall was more intact than that of the site with atheroma. Part of the wall of the coronary artery was seen to be made up of only the adventitia. The lumen
<table>
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<tr>
<th>Case</th>
<th>Description</th>
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<tbody>
<tr>
<td>Case 1</td>
<td>Intimal desquamation, thrombus</td>
</tr>
<tr>
<td>Case 2</td>
<td>Intimal disruption and desquamation, thrombus</td>
</tr>
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<td>Case 3</td>
<td>Intimal disruption and desquamation, thrombus</td>
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<td>Case 4</td>
<td>Intimal disruption and desquamation, thrombus</td>
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<tr>
<td>Case 5</td>
<td>Intimal and medial disruption, medial dissection, intimal desquamation, thrombus</td>
</tr>
<tr>
<td>Case 6</td>
<td>Intimal and medial disruption, medial dissection, intimal desquamation, thrombus</td>
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<td>Case 7</td>
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<tr>
<td>Case 8</td>
<td>Medial dissection, intimal disruption, thrombus</td>
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**TABLE II** HISTOPATHOLOGICAL FINDINGS OF THE CORONARY ARTERY AT THE SITE OF PTCA

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<td>Case 9</td>
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<td>Case 10</td>
<td>Intimal desquamation, release of atheroma</td>
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<td>Case 11</td>
<td>Intimal disruption</td>
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<td>Case 12</td>
<td>Fragmentation of intimal elastic fibers, loss of internal elastic membrane, proliferation of intimal cells</td>
</tr>
<tr>
<td>Case 13</td>
<td>Fibrous plaque</td>
</tr>
<tr>
<td>Case 14</td>
<td>Intimal and medial disruption, proliferation of intimal cells</td>
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</table>

(L) was found to be restenosed with excessively proliferated intimal cells (Figs. 5C & D).

**Case 10:** R.T. A 67-year-old man

This patient was admitted to the hospital for evaluation of old left ventricular posterolateral myocardial infarction and acute anteroseptal myocardial infarction. CAG was immediately performed, showing a 90% narrowing of segment 6 of the left anterior descending artery (Fig. 6A). PTCA was performed, and the narrowing was reduced to 25% (Fig. 6B). In addition to intra-aortic balloon pumping, hemodialysis was conducted for insufficient diuresis. Sixteen days after the onset of acute myocardial infarction, however, the patient died from pneumonia combined with severe congestive heart failure.

Necropsy findings: Heart weight was 400g. The necropsy showed the presence of old infarction in the posterolateral wall of the left ventricle, and of relatively fresh infarction in the left ventricular anterior wall and the anterior portion of the ventricular septum. All three vessels of the coronary artery were occluded or significantly stenosed. There was a 50% narrowing of the coronary artery at the site of PTCA (Fig. 6D). Figure 6C shows an area 3–4 mm from the site of PTCA. Atheroma was covered with intimal collagen fibers. In the lumen, indicated by "L", barium contrast medium (I) used in coronary arteriography, performed immediately after the death of this patient, was observed. As seen in Fig. 6D which shows the coronary artery at the site of PTCA, another lumen like channel L' was identified, besides the lumen L. Figure 6E is a detail of the area indicated by the mark * in Fig. 6D. In the area indicated by arrow D, destroyed intimal collagen fibers were observed, as was deposition of the contrast material (I) and deposition of a fresh thrombus (Th) over the surface of the lumen L'. The contrast material (I) was deposited diffusely, though sparsely, over the surface of the lumen L'. The false-lumen, L', was considered to have already been formed before postmortem coronary arteriography. If the false-lumen, L', were an artifact created during the preparation of the tissue specimens, the contrast material would not have been found deposited diffusely in this area. We believe that the atheroma in channel L' had collapsed and had spread into the pre-existing lumen.

**Case 12:** K.I. A 56-year-old man

This patient had unstable angina pectoris. CAG disclosed an approximately 80% narrowing of segment 7 of the left anterior descending artery (Fig. 7A). PTCA was performed, thereby reducing the narrowing to 50% (Fig. 7B), and there was an improvement in both subjective and...
Treatment of Ischemic Heart Disease

A. Disruption  B. Dissection  C. Desquamation

D. Release of Atheroma

Fig. 9. Mechanism of Luminal Enlargement in PTCA
A: Intimal and medial disruption. Where the lumen is eccentric, intimal and medial disruption occurs in the arterial wall located opposite the atheroma even though this wall is more normal than that of the site with atheroma.
B: Medial dissection.
C: Intimal desquamation. Intimal desquamation produces a slight enlargement of the artery, though it may cause embolism in the peripheral portion.
D: Release of atheroma into the lumen. This is observed in Case 4.

objective clinical symptoms. This patient, however, suffered from depression, and committed suicide by hanging himself seven months after PTCA.

Necropsy findings: Heart weight was 295g. Scars were found sporadically in the inner layer of the myocardium of the left ventricular anterior wall and the ventricular septum. The coronary artery at the site of PTCA revealed a 75% segmental narrowing, which was approximately 5 mm long (Fig. 7C). No compression of the atheroma was seen (Fig. 7C), and there was fragmentation of elastic fibers, which had proliferated in the intima, and a loss of the internal elastic membrane at the same site (Figs. 7C & D). An excessive proliferation of intimal cells was present at the site of the fragmented elastic fibers (Figs. 7E & F).

Case 14: M.H. A 60-year-old woman
This patient had angina pectoris and aortic aneurysm. PTCA reduced a 90% narrowing of segment 7 of the left anterior descending artery to 10% (arrow in Figs. 8A & B). On the same day, surgical correction was performed for aortic aneurysm. Later, condition having improved, the patient was discharged from hospital. Three months after PTCA, however, she developed dysphagia and underwent surgery again to correct aortic aneurysm. One month after this surgery, she developed pneumonia and died.

Necropsy findings: At necropsy, the coronary artery at the site of PTCA revealed focal damage to the arterial wall with intimal and medial disruption, located opposite the site with atheroma, even though this wall was more intact than that at the site with atheroma (Figs. 8C & D). Also present was a marked proliferation of intimal cells (Figs. 8E & F).

Table II shows list of morphological changes observed in the coronary artery that may have resulted from PTCA. Of the eight patients who died shortly after PTCA, two had intimal and medial disruption in the arterial wall located opposite the atheroma, even though the former wall was almost normal. Dissection of the media was performed in four patients, while intimal desquamation was carried out in six. All the patients manifested fresh thrombus formation. Also, among the six patients who survived for a long time after PTCA, two had intimal and medial disruption in the arterial wall opposite the site that had atheroma. One had dissection of the media, and one had intimal desquamation. In one patient, release of atheroma into the lumen was suspected. Three patients revealed proliferation of intimal cells, indicating that restenosis had occurred. No compression of atheroma¹¹,¹³ was observed in any of the 14 patients.

Lesions which are connected with luminal enlargement of the coronary artery are summarized in Fig. 9. Every tissue specimen showed more than one of the lesions.

DISCUSSION
1. Mechanism of Luminal Enlargement of the Coronary Artery
A total of 14 cases with either angina pectoris or myocardial infarction in whom PTCA was performed and whose necropsied coronary arteries at the site of PTCA were investigated histopathologically have been reported⁷–⁹ (Table III). Of the 14 cases, seven patients died less than two weeks after PTCA, and the other seven died two weeks or more after PTCA. In a separate study from these 14 cases, we studied our own 14 cases (however, our Case 8 is the same as the case reported by Mizuno⁵). In the whole group of 27 cases, only seven patients were considered to have died directly from complications resulting

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from PTCA. It is thought that morphological changes described in Tables II and III are a common consequence of PTCA. Although the mechanism of luminal enlargement in PTCA had been considered to be a compression of atheroma, similar to the packing down and hardening of snow after having been trodden upon, no compression of atheroma was observed in any of the 27 patients. Experimental studies of coronary angioplasty in cadaver hearts and studies performed in animals suggested two mechanisms of angioplasty: medial dissection and intimal and/or medial disruption. Besides these mechanisms, collapse of atheroma at the site of PTCA and its release into the lumen was also postulated. This mechanism was suspected in our Case 10. It is, however, difficult to prove the release of atheroma into the vascular lumen histopathologically. Sanborn et al. induced atherosclerosis in the aorta and iliac arteries of eight rabbits, and performed angioplasty in the stenotic vessels. They used polarized microscopy to determine whether embolic debris was present in the perfusate of the vessels. In one of the eight rabbits, lipid debris from the plaque was present, which was accounted for by transmural angioplasty. Block et al. conducted a very similar experiment, and reported that in two out of five rabbits, a few single endothelial cells and cholesterol crystals were identified in effluents after angioplasty.

2. Restenosis

It is generally recognized that restenosis occurs in 30%–40% of patients who undergo PTCA. It seems that two mechanisms of restenosis after PTCA exist: organization of thrombi and reconstruction of the intimal wall of the artery. In this study, in all eight patients who died shortly after PTCA, fresh thrombus formation was observed (Table II). It seems that such fresh thrombi may lead to the occurrence of irreversible stenosis of the artery shortly after the procedure.

As for reconstruction of the intimal wall of the artery, a variety of postulations can be considered, such as the “response to injury hypothesis of atherosclerosis” put forward by Ross et al. When endothelial injury or desquamation occurs, platelets immediately adhere to, and become aggregated at, the affected site. Afterwards, platelet derived growth factor (PDGF) is released from alpha granules of the platelets, and smooth muscle cells migrate from the media to

<table>
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<th>Medial dissection, intimal disruption, thrombus formation, fragmentation of smooth muscle cells</th>
<th>Medial dissection, intimal disruption, proliferation of smooth muscle cells</th>
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<tr>
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<td>Block²</td>
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<tr>
<td>3</td>
<td>Saffiz²</td>
<td>Male (43)</td>
<td>Medial dissection, intimal disruption, thrombus formation</td>
<td></td>
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<tr>
<td>4</td>
<td>Weller²</td>
<td>Male (61)</td>
<td>Medial dissection, intimal disruption, dissection</td>
<td></td>
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</tr>
<tr>
<td>5</td>
<td>Mizuno²</td>
<td>Female (65)</td>
<td>Medial dissection, intimal disruption, thrombus formation, fragmentation of smooth muscle cells</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6</td>
<td>Austin²</td>
<td>Male (26)</td>
<td>Medial dissection, intimal disruption, thrombus formation</td>
<td></td>
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</tr>
<tr>
<td>7</td>
<td>Soward²</td>
<td>Female (65)</td>
<td>Medial dissection, intimal disruption, dissection</td>
<td></td>
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</tr>
</tbody>
</table>

*Male

**Female

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*Japanese Circulation Journal Vol. 52, September 1987*
the intima, thereby causing hypertrophy of the intima with proliferated smooth muscle cells. In most patients who have undergone PTCA, an area of arterial endothelium is abraded by means of a balloon catheter. The balloon inflation sometimes causes medial disruption or dissection. It is, therefore, reasonable to postulate that the mechanism of restenosis is the "response to injury hypothesis of atherosclerosis". Smooth muscle cells are indispensable in repairing the injured arterial walls, but an excessive proliferation of intimal smooth muscle cells leads to intimal hypertrophy, i.e., restenosis.

As mentioned above, it is possible to conjecture that the mechanisms of restenosis after PTCA are organization of thrombus and reconstruction of the intimal wall of the artery. The ultimate validity of this conjecture, however, remains unanswered. Further investigation is required to determine in which patients and by what mechanism restenosis occurs.

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